

Remarks

In view of the above amendments and the following remarks, favorable reconsideration of the outstanding office action is respectfully requested.

Attached hereto is a page entitled "Version of Markings to Show Changes Made." Claims 1-2, 5, 8-42 remain in this application. Claims 1, 5, and 8, have been amended. Claims 4, 6, and 7 have been canceled.

1. Allowed Claims/Subject Matter

Applicant notes with appreciation the Examiner's indication that the subject matter of claims 8-16, 18-20, 23, 24, 27, 28, 31, 36-38 are objected to, but would be allowable if rewritten in independent form. As allowable subject matter, the Examiner writes that the cited references taken alone or in combination, fail to suggest or teach a specific apparatus whose structure has a Y-shaped element including a sensing area, or a system that detects change in the far field diffraction pattern generated by three laterally spaced openings as set forth in the claims.

2. Nature of the Invention

The present invention involves a device for sensing the interactions between or among biological or chemical molecules by means of monitoring the diffusion of analytes across a selectively permeable barrier or membrane. The barrier forms part of a boundary between a first and second region or compartment. Ligand or probe molecules along with receptor or target molecules are contained in the first compartment. The selectively permeable barrier permits ligand molecules to pass through from the first to the second compartment, but either retards or prevents passage of receptors. A ligand molecule and its respective receptor molecule are permitted to react. An optical detector is located proximal to the barrier at a sensing area, preferably on the second-region side. The diffusion or leaching of the ligand, receptor and/or their conjugate over the sensing area is monitored over time. According to an example, as analyte amounts increase, this may be indicated by a change in absorbance of light in the sensing area or second compartment.

The binding affinity of a ligand for a receptor (i.e., probe and target) may be determined from the diffusion rate of the molecules amidst reactivity. The distance a species travels due to diffusion is a function of time and its diffusion coefficient. For examples, large

differences between a ligand and its receptor can be used to determine the ligand-receptor binding based on the rate of diffusion.

Generally, diffusion rate is a function of the amount of time required to reach a steady-state at certain concentration. If, for instance, a mixture of a ligand (e.g., drug molecule) and receptors (e.g., proteins) at a specific concentration ratio are placed proximate to a sensing area, the diffusion pattern from or towards the sensing area will be influenced by whether the ligand and the receptors bind. In the case of non-binding species, the detector will sense first the movement of smaller molecules with higher mobility, before the movement of larger molecule species because of their slower diffusion kinetics. Thus, when the ligand and receptor do not bind or interact two widely spaced signals can be detected. When the ligand does bind the receptor, however, the smaller ligand molecule will not be detected as a singly diffusing species, but a point later than compared with unbound ligand signal.

An advantage of the invention is that the ligand, receptor, or any of the constituents require no labeling chemistry for the binding analysis. Another advantage is that the invention enables manufacture of relatively simple sensor devices that may be miniaturized to small dimensions. Moreover, the invention does not require complex microfluidics, which makes possible the prospect of fairly compact, high-density, high-throughput devices, such as for drug screening.

The foregoing generalized explanation of the present invention should not be construed as limiting the invention or its mechanisms, which are discussed more fully in the Specification.

3. § 102 Rejections

The Examiner rejects claims 1-3, 32 and 39 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,151,123 (Nielsen '123 patent). In relation to claims 1, 2, 32 and 39, the Examiner alleges that Nielson '123 teaches a method and apparatus for measuring or characterizing the relative and absolute properties of an arrays of diverse materials. With regard to claim 3, the Examiner asserts that since the reference apparatus can have an array of materials that differ slightly in concentration, then the reference suggests that the concentration of material can be measured.

To be anticipatory under 35 U.S.C. § 102, a patent reference must "describe" every element recited in the claims at hand. The Nielsen '123 patent neither teaches nor suggests the invention as claimed. As the Examiner will appreciate from explanation in the foregoing section, the reference has been misread – focusing on certain common words or phrases, but failing to understand the overall context of the patent. Although the reference mentions "interrogating a substrate having an array of diverse materials in predefined regions thereon," careful reading indicates that the Nielsen '123 patent describes a method and apparatus for screening materials largely by means of micro-calorimetry. The substrate is subjected to a temperature ramp. (Claim 1) The materials are "combined with at least one environment-sensitive optical probe," such as a dye, and the optical behavior of the probes are monitored by "illuminating the samples and varying the temperature of the substrate." A property of each sample is measured as a function of temperature. "[C]ontrolling the environment is a function of varying the temperature of the system." (Col. 4, lines 38-67, and Col. 5, lines 1, 35-40)

Rather than anticipate, the cited reference discloses or suggests elements that are either opposite from those desired or are detrimental to the present invention. In the present invention, temperature of the system preferably should not vary significantly, rather its should be rather stable. Variable temperatures will cause material change in the refractive index. For example, water changes its optical refractive index (n_{iu}) by $10^{-4} n_{iu}/^{\circ}\text{C}$. Changes in refractive indices is detrimental to optical detection sustained over time, since readings at different temperatures would be difficult to compare according to the present invention. In addition, variations in temperature can affect change in the diffusion pattern or rate of particles passing before the sensing region. Thus, in view of these reasons, Applicant submits that the Examiner properly should withdraw the present rejection.

4. § 103 Rejections

The Examiner rejects claims 4-7, 16, 21, 22, 25, 26, 29, 33, 35, and 40-42 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,151,123 (Nielsen '123) in view of U.S. Patent No. 5,776,674 (Ulmer '674). The Examiner acknowledges that Nielsen '123 fails to specifically teach or fairly suggest that the device comprises first and second compartments; nevertheless, alleges that it would have been obvious to one of ordinary skill in the art to apply the teachings of Ulmer '674 to the teachings of Nielsen '123. Further, the

Examiner rejects claims 30 and 34 as being unpatentable over Nielsen '123 as modified by Ulmer '674, and further in view of U.S. Patent No. 5,007,737 (Hirleman '737).

Applicant submits that a *prima facie* case of obviousness has not been made. Neither the Nielsen '123 nor Ulmer '674 references, either viewed together or in combination with the Hirleman '747 patent, suggests the claimed invention.

First, as Applicant explained above, the Nielsen '123 patent is not an appropriate reference under Sections 102, nor is it now under Section 103. The reference simply teaches away from the present invention. Second, like the Nielsen '123 patent, the Ulmer '674 patent contains some common words and phrases, but it does not teach or suggest a device for detecting the interaction of molecules through a function of their diffusion across a matrix or membrane. Rather, at best the reference is non-analogous art. The Ulmer '674 patent describes a system that employs an optical trap, also known as "optical tweezers." So-called optical tweezers are used to trap a particle near the focus of a strongly focused light beam, and move the particle along, through a succession of different regions (i.e., "puddles") on an optically-flat surface. Within each region, the trapped particle may undergo interaction for chemical or biochemical processes.

Moreover, as the Examiner notes, the Nielsen '123 reference does not provide a great detail on the structure of the apparatus. This absence of details indicates a technical gap, the bridging of which would not be obvious to one skilled in the art. For obviousness purposes, the references themselves must suggest that elements can reasonably be combined. In *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992), the court reiterated that "[t]here must be some reason, suggestion or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination" and "[t]hat knowledge cannot come from the applicant's invention itself." The absence of such details is a failing of the reference to suggest or teach that the patents can or should be combined to produce the present invention as claimed, let alone adaptation, as the Examiner proposes. A mere reading of the Nielsen '123 and Ulmer '674 references would not lead a person of skill in the art to conclude that the present invention was obvious, when the references are either silent or discuss a different, non-analogous mechanism.

Third, the courts recognize that an invention will not be deemed obvious when one or more of the combined references "teach away" from the invention. The *prima facie* case of

obviousness based on a combination of the Nielsen '123, Ulmer '674, and Hirleman '737 patents can not stand either. Whereas the Hirleman '737 reference must be combined with the first two references, and whereas Applicant has already shown that Nielsen '123 and Ulmer '674 either teach away or is different from the present invention, then Applicant's invention cannot be deemed obvious.

For the foregoing reasons, Applicant requests that the present rejection be withdrawn.

5. Conclusion

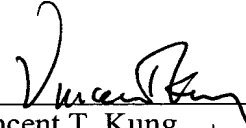
Based upon the above amendments, remarks, and papers of record, Applicant believes the pending claims of the above-captioned application are in allowable form and patentable over the prior art of record. Applicant respectfully requests reconsideration of the pending claims and a prompt Notice of Allowance thereon.

Applicant believes that a one-month extension of time is necessary to make this Response timely. Should Applicant be in error, Applicant respectfully requests that the Office grant such time extension pursuant to 37 C.F.R. § 1.136(a) as necessary to make this Reply timely, and hereby authorizes the Office to charge any necessary fee or surcharge with respect to said time extension to the deposit account of the undersigned firm of attorneys, Deposit Account 03-3325.

Please direct any questions or comments to Vincent T. Kung at 607-974-0608.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. A molecular detection apparatus comprising:
a first compartment containing at least a ligand or a receptor;
a second compartment adjacent said first compartment;
a boundary area disposed between said first and second compartments;
a sensing area; and
means for detecting the diffusion of a molecule proximate the sensing area.
4. ~~The molecular detection apparatus of claim 3, wherein the means for detecting diffusion of the molecule comprises a first compartment.~~
5. The molecular detection apparatus of claim 4~~1~~, wherein the first compartment contains a matrix material and a receptor molecule.
6. ~~The molecular detection apparatus of claim 5, further comprising a second compartment adjacent the first compartment and a boundary area disposed between the first and second compartments.~~
7. ~~The molecular detection apparatus of claim 6, wherein the first compartment also contains a ligand molecule.~~
8. The molecular detection apparatus of claim 7~~1~~, wherein the ligand molecule is smaller than the receptor molecule and wherein the boundary area includes a membrane operative to allow ligand molecules to pass therethrough and to prevent passage of receptor molecules.